STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 110572

TO: Anand Desai Location: CM-1/9B01 Art Unit: 1653 Thursday, December 18, 2003 Case Serial Number: 09/888072	From: Mary Hale Location: Biotech/Chem Library CM1-1E01 Phone: 308-4258 Mary.Hale@uspto.gov

Search Notes

Searched the elected species
Searched camptothecin with part of the structure.

Inventor and text search included

Questions? Please feel free to call me.
Thanks.
M

Access DB# 110592

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Anand Desai Examiner #: 79924 Date: 12-16-03
Art Unit: 1653 Phone Number 305-4443 Serial Number: 09/888,072
Mail Box and Bldg/Room Location: CM-1, 9B01 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

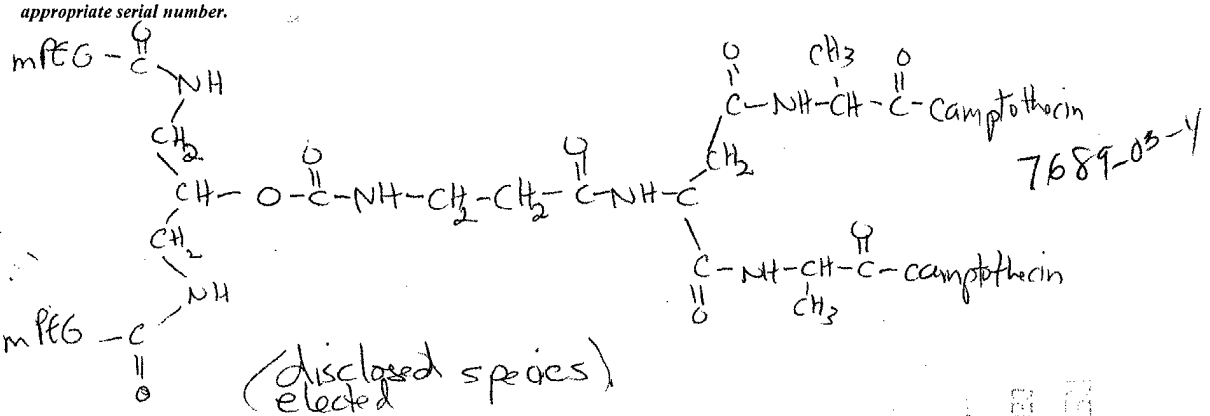
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Biodegradable High Molecular weight polymeric linkers and their conjug

Inventors (please provide full names): ~~Richard Greenwald~~ & Hong Zhao
Richard Greenwald

Earliest Priority Filing Date: 4/17/1998

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**



7689-03-4

(disclosed elected species)

mPEG: mono-methyl-terminated polyethylene glycols

Call me if you have question. (703) 305-4443

14:10
14:28

****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
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Date Completed: 12/19	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	Fulltext		Sequence Systems	
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PTO-1590 (8-01)

Desai
888072

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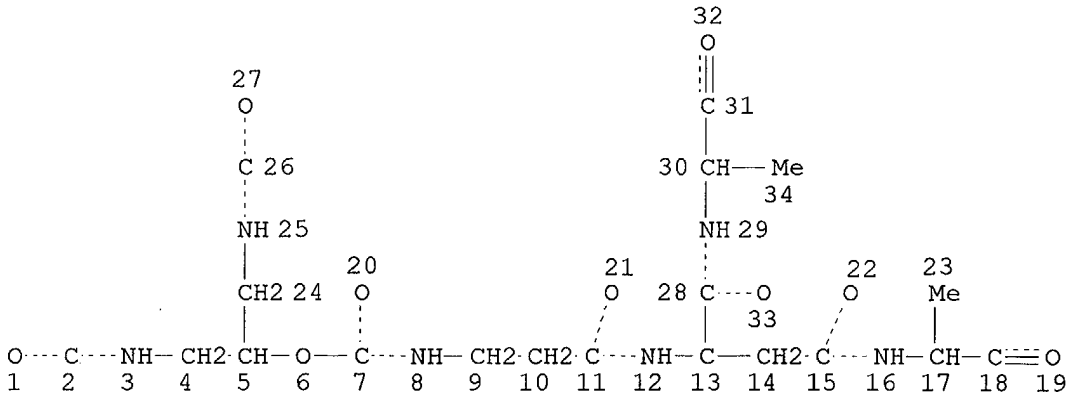

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DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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100.0% PROCESSED     88 ITERATIONS                              1 ANSWERS
SEARCH TIME: 00.00.01
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RN   391612-50-3  REGISTRY
CN   Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, ether with
     N-[[2-[(hydroxyacetyl)amino]-1-[[(hydroxyacetyl)amino]methyl]ethoxy]carbon
     yl]-β-alanyl-L-aspartoyl-L-alanine bis[(4S)-4-ethyl-3,4,12,14-
     tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl]
     ester (2:1) (9CI)  (CA INDEX NAME)
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CI   PMS
PCT  Polyether
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPATFULL
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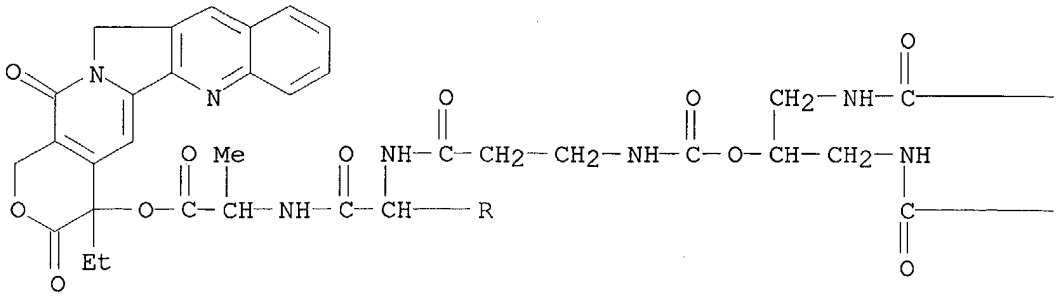
Searched by: Mary Hale 308-4258 CM-1 1E01

PAGE 1-A



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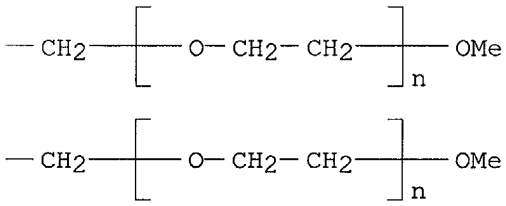

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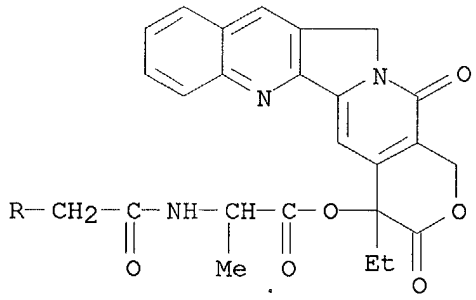

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:123688 Preparation of biodegradable high molecular weight polymeric linkers and their drug conjugates. Greenwald, Richard B.; Zhao, Hong (USA). U.S. Pat. Appl. Publ. US 2002009426 A1 20020124, 39 pp., Cont.-in-part of U.S. 6,251,382. (English). CODEN: USXXCO. APPLICATION: US 2001-888072 20010622. PRIORITY: US 1998-PV82105 19980417; US 1999-293557 19990415.

AB The present invention includes polymeric transport systems such as prodrugs of polyoxyethylene with pharmaceuticals such as daunorubicin, and camptothecin. A solution of of m-PEG acid, diaminopimelic aspartic acid camptothecin TFA salt, a 50% solution of 1-propanephosphonic acid cyclic anhydride in EtOAc and N-dimethylaminopyridine in dry dichloromethane was stirred at room temperature overnight followed by washing with 1% aqueous NaHCO3 and

Searched by: Mary Hale 308-4258 CM-1 1E01

0.1N HCl solution The solvent was removed , and the residue was crystallized from
2-propanol to yield the product.

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L4                STR
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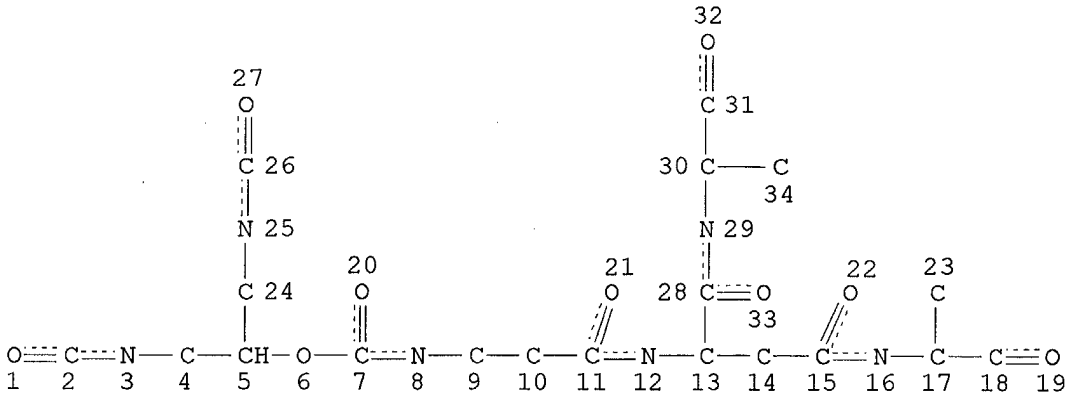

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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STEREO ATTRIBUTES: NONE
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100.0% PROCESSED     88 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01


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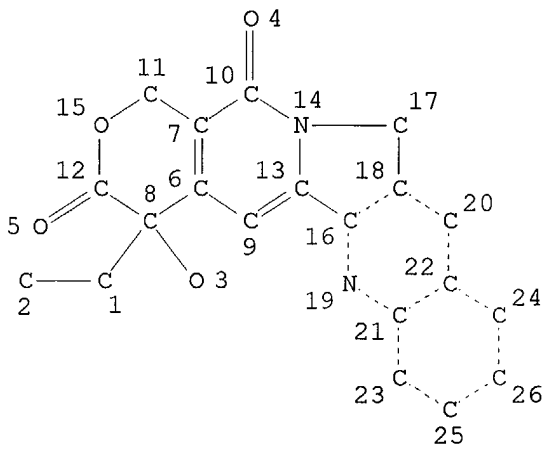
Searched by: Mary Hale 308-4258 CM-1 1E01



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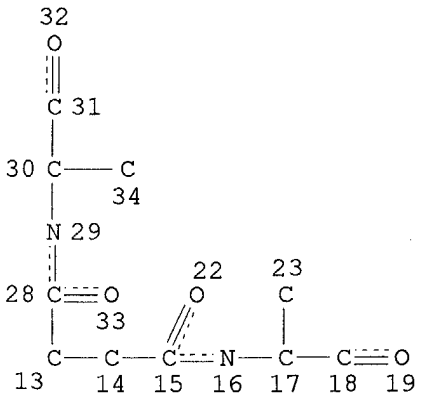

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100.0% PROCESSED 39 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

Searched by: Mary Hale 308-4258 CM-1 1E01

L16 2 L15 NOT L3

L16 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN 396134-25-1 REGISTRY
CN L-Aspartamide, N-[(1,1-dimethylethoxy)carbonyl]-L-aspartoylbis[N1,N4-bis[2-[2-[[[[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl]oxy]carbonyl]oxy]ethoxy]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C117 H117 N15 O36
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

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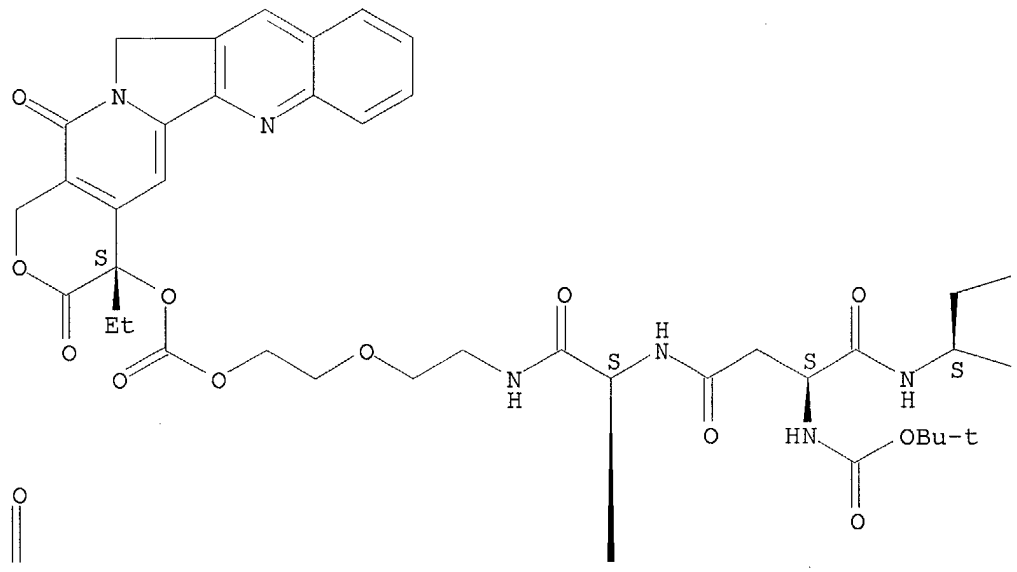

Searched by: Mary Hale 308-4258 CM-1 1E01

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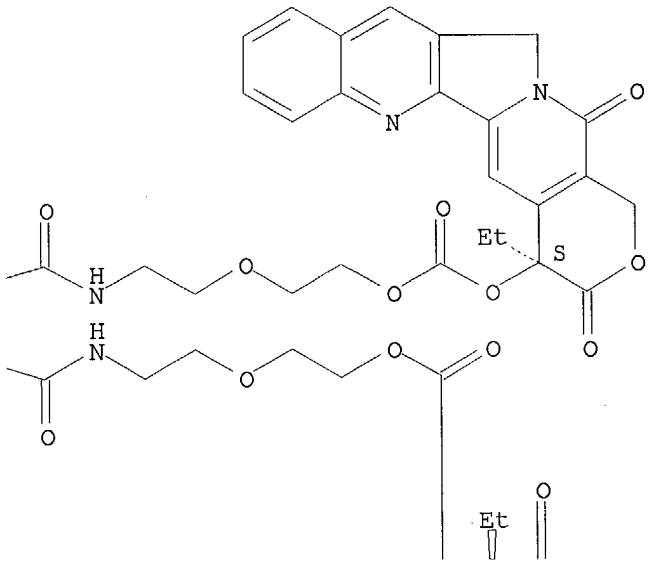

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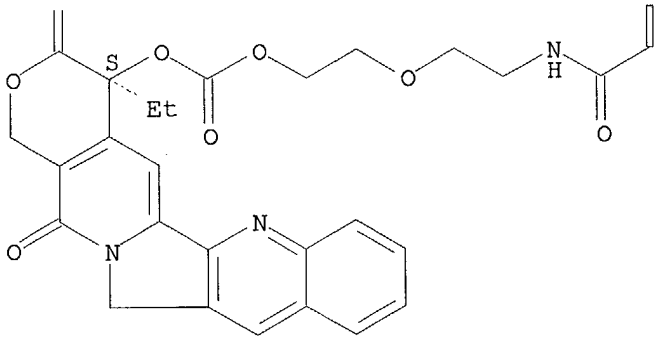

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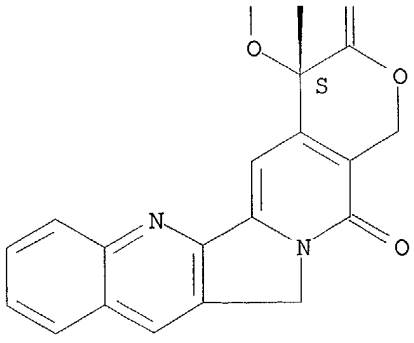

Searched by: Mary Hale 308-4258 CM-1 1E01

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:172758 Terminally-branched polymeric linkers containing extension moieties for prodrug conjugates. Greenwald, Richard B.; Choe, Yun H. (USA). U.S. Pat. Appl. Publ. US 2002015691 A1 20020207, 32 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-823296 20010329. PRIORITY: US 2000-PV193931 20000331.

AB The present invention relates to polymer-based (e.g., PEG) conjugates having increased therapeutic payloads. In particular, the invention relates to the use of extension moieties which increase the efficiency of the loading of drugs onto the polymeric carriers. A variety of prodrugs were prepared from ara-C and PEG derivs. by using spacer groups. The prodrug demonstrated better antitumor activity than ara-C alone. The prodrug produced complete tumor regression.

L16 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN 396134-21-7 REGISTRY
CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, ether with hydroxyacetyl-L-aspartoylbis[N1,N4-bis[2-[2-[[[[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl]oxy]carbonyl]oxy]ethoxy]ethyl]-L-aspartamide] (9CI) (CA INDEX NAME)
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PCT Polyether
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

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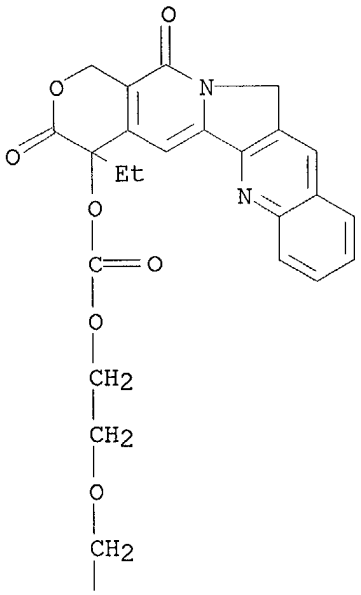

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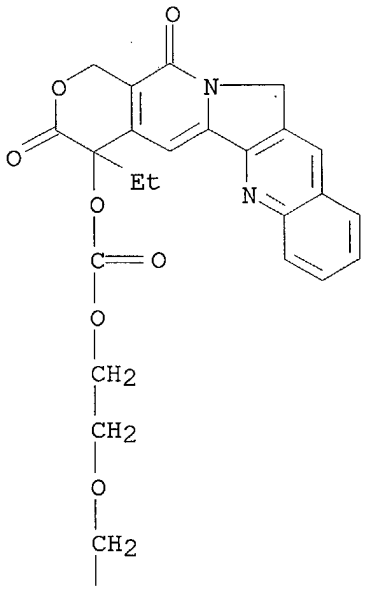

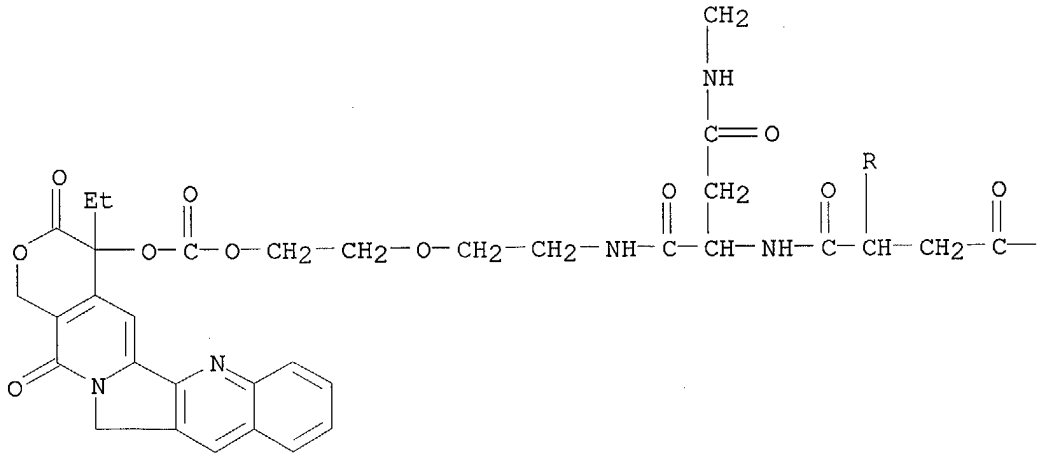

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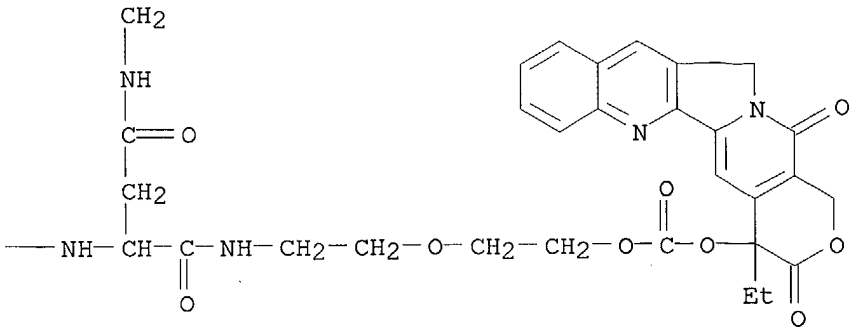

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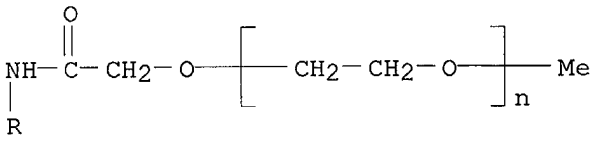

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:172758 Terminally-branched polymeric linkers containing extension moieties for prodrug conjugates. Greenwald, Richard B.; Choe, Yun H. (USA). U.S. Pat. Appl. Publ. US 2002015691 A1 20020207, 32 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-823296 20010329. PRIORITY: US 2000-PV193931 20000331.

AB The present invention relates to polymer-based (e.g., PEG) conjugates having increased therapeutic payloads. In particular, the invention relates to the use of extension moieties which increase the efficiency of the loading of drugs onto the polymeric carriers. A variety of prodrugs were prepared from ara-C and PEG derivs. by using spacer groups. The prodrug demonstrated better antitumor activity than ara-C alone. The prodrug produced complete tumor regression.

=> fil medl,hcaplus,biosis,embase,jicst;s polymer? link? and biodegrad?

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	624.44	628.85

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L18 9 FILE HCAPLUS
L19 7 FILE BIOSIS
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L29 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
2002:72705 Document No. 136:123688 Preparation of **biodegradable** high molecular weight **polymeric linkers** and their drug conjugates. **Greenwald, Richard B.; Zhao, Hong** (USA). U.S. Pat. Appl. Publ. US 2002009426 A1 20020124, 39 pp., Cont.-in-part of U.S. 6,251,382. (English). CODEN: USXXCO. APPLICATION: US 2001-888072 20010622. PRIORITY: US 1998-PV82105 19980417; US 1999-293557 19990415.

AB The present invention includes polymeric transport systems such as prodrugs of polyoxyethylene with pharmaceuticals such as daunorubicin, and camptothecin. A solution of of m-PEG acid, diaminopimelic aspartic acid camptothecin TFA salt, a 50% solution of 1-propanephosphonic acid cyclic anhydride in EtOAc and N-dimethylaminopyridine in dry dichloromethane was stirred at room temperature overnight followed by washing with 1% aqueous NaHCO3 and 0.1N HCl solution The solvent was removed , and the residue was crystallized from 2-propanol to yield the product.

L29 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
2001:468173 Document No. 135:66230 **Biodegradable** high molecular weight **polymeric linkers** and their conjugates. **Greenwald, Richard B.**; Martinez, Anthony J.; Choe, Yun H.; Pendri, Annapurna (Enzon, Inc., USA). U.S. US 6251382 B1 20010626, 32 pp. (English). CODEN: USXXAM. APPLICATION: US 1999-293557 19990415. PRIORITY: US 1998-PV82105 19980417.

AB Methods of preparing polymer conjugates of a biol. active compound having an

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available hydroxy (or amine) group which undergoes a substitution reaction, as prodrugs, and methods of treatment using the same are described. A biol. active compound is a member of the group consisting of antitumor, cardiovascular, anti-infective, antifungal, antianxiety, gastrointestinal, central nervous system-activating, analgesic, fertility or contraceptive, anti-inflammatory, steroidal, anti-uremic, vasodilating and vasoconstricting agents, and a polymer is a polyalkylene oxide, e.g., polyethylene oxide. For example, mPEG was conjugated with diaminopimelic aspartic camptothecin or with diaminopimelic camptothecin to yield 0.8 g (80% yield) and 1.85 g (93% yield) of products, resp.

L30 2 FILE MEDLINE
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L32 6 FILE BIOSIS
L33 3 FILE EMBASE
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TOTAL FOR ALL FILES
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L36 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
2003:678871 Document No. 139:214915 Hydrolytically-degradable alkylene oxide polymers, preparation, hydrogels, and biological conjugate delivery system. Bentley, Michael D.; Harris, J. Milton; Zhao, Xuan; Battle, William Dudle, III (Nektar Therapeutics Al, Corporation, USA). PCT Int. Appl. WO 2003070805 A1 20030828, 62 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US5113 20030214. PRIORITY: US 2002-PV357350 20020215.

AB A water-soluble, nonpeptidic polymer comprises ≥2 alkylene oxide-based oligomers linked together by hydrolytically degradable linkages such as carbonates. Typically, the oligomer portion of the polymer is an amphiphilic triblock copolymer having a central propylene oxide block or butylene oxide block positioned between 2 ethylene oxide blocks. The polymer can be hydrolytically degraded into oligomers under physiol. conditions. In aqueous media, the polymer preferably forms thermally-reversible, hydrolytically-degradable hydrogels that can be used for PEGylated drug delivery and related biomedical applications.

L36 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
2003:558232 Development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application. Sen Gupta, A.; Lopina, S. T. (Department of Chemical Engineering, The University of Akron, Akron, OH, 44325, USA). Materials Science Forum, 426-432(Pt. 4, THERMEC'2003), 3261-3266 (English) 2003. CODEN: MSFOEP. ISSN: 0255-5476. Publisher: Trans Tech Publications Ltd..

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AB Synthetic **biodegradable** polymers, using natural metabolites as monomers, have been established as an effective class of biomaterials. The **biodegrdn.** of such polymers into the corresponding naturally metabolizable monomers and their derivs. renders the polymers biocompatible. Amino acid "monomers" seem a logical choice for the development of such biomaterials. Despite their biocompatibility, use of poly(amino acids) is limited by practical difficulties like insoly. in common organic solvents, thermolability, unpredictable water intake and swelling behavior, etc., which have been traced back to the highly crystalline structure and hydrogen bonding induced by the sequence of amide(peptide) bonds in the polymer backbone. Hence introduction of non-amide bonds alternating with the amide(peptide) link in the poly(amino acid) backbone is being investigated as one of the ways to circumvent such properties. The resulting polymer would be called a "pseudo"poly(amino acid). The non-peptide link is expected to impart properties that are potentially favorable for biomaterial applications. In this paper development of such "pseudo"poly(amino acids) starting from natural amino acid L-tyrosine, is described. The process involves the synthesis of a model diphenolic compound containing a peptide link, from L-tyrosine. This compound is further polymerized through the phenolic terminals using conventional tools of polymer chemical to produce non-peptidic **polymeric linkages.** The resulting polymers, namely, a polycarbonate and a polyphosphate are characterized for their physicochem. properties. Based upon preliminary investigation of these properties, potential biomaterial applications of such polymers are discussed.

L36 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2000:292073 Document No.: PREV200000292073. Polymer-platinum compounds. Duncan, Ruth [Inventor, Reprint author]; Ferruti, Paolo [Inventor]; Evagorou, Evagoras G. [Inventor]. London, UK. ASSIGNEE: Access Pharmaceuticals, Inc., Dallas, TX, USA. Patent Info.: US 5985916 November 16, 1999. Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 16, 1999) Vol. 1228, No. 3. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB A polymer-platinum compound for use in tumor treatment is described. The compound is composed of a **biodegradable** diamido-diamine **polymer linked** to a platinum species. The platinum species is released from the polymer to yield a platinum species having anti-tumor activity.

L36 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
1998:708929 Document No. 129:339862 Diamido-diamine polymer-platinum compounds for tumor treatment, and preparation thereof. Duncan, Ruth; Ferruti, Paolo; Evagorou, Evagoras G. (Access Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9847496 A2 19981029, 32 pp. DESIGNATED STATES: W: AU, CA, JP, MX, TR; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US7659 19980415. PRIORITY: US 1997-44701 19970418.
AB A polymer-platinum compound for use in tumor treatment is described. The compound is composed of a **biodegradable** diamido-diamine **polymer linked** to a platinum species. The platinum species is released from the polymer to yield a platinum species having anti-tumor activity.

L36 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
1991:663330 Document No. 115:263330 Biodistribution of trans-1,2-diaminocyclohexane-trimellitatoplatinum(II) attached to macromolecular carriers. I. Poly(hydroxyethyl-D,L-asparagine) carrier. Filipova-Voprsalova, Marie; Drobnik, Jaroslav; Sramek, Blahoslav; Kvetina, Jaroslav (Inst. Exp. Biopharm., Hradec Kralove, Czech.). Journal of

Controlled Release, 17(1), 89-97 (English) 1991. CODEN: JCREEC. ISSN: 0168-3659.

AB Two types of macromol. drug forms of the second generation platinum antitumor drug 4-carboxyphthalato-(trans-1,2-diaminocyclohexane)platinum(II) (TMA) were prepared with nonbiodegradable carriers derived from racemic poly(N4-substituted aspartamide): AN type was prepared from N-(2-hydroxyethyl) and AR type from N-(2-hydroxypropyl) derivative by acylation with trimellitato residues, thus yielding primary and secondary ester bonds resp. Plasma levels, urinary excretion and organ deposition of platinum were followed after administration into rats. When compared with free TMA both types of macromol. forms showed a retardation effect in platinum pharmacokinetics with the most pronounced differences using the AR type. Considering all possible **biodegradable** bonds in the polymeric drug forms the nature of the drug-**polymer link** seemed to play an important role in the kinetics of drug release as revealed by the differences between the AN and AR type.

L36 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 2

1990:145395 Document No. 112:145395 Anticancer agents coupled to N-(2-hydroxypropyl)methacrylamide copolymers. 3. Evaluation of adriamycin conjugates against mouse leukemia L1210 in vivo. Duncan, Ruth; Hume, Isabella C.; Kopeckova, Pavla; Ulbrich, Karel; Strohalm, Jiri; Kopecek, Jindrich (Dep. Biol. Sci., Univ. Keele, Keele/Staffordshire, ST5 5BG, UK). Journal of Controlled Release, 10(1), 51-63 (English) 1989. CODEN: JCREEC. ISSN: 0168-3659.

AB N-(2-Hydroxypropyl)methyacrylamide (HPMA) copolymers were synthesized containing adriamycin (ADR) and in certain cases fucosylamine or galactosamine residues. Drug was attached to polymer via **biodegradable** (-Gly-Phe-Leu-Gly) or nonbiodegradable (-Gly-Gly) oligopeptide side-chains. Fucosylamine and galactosamine were included to promote conjugate targeting to L1210 cells and hepatocytes, resp. Although free ADR (5 mg/kg) can increase the mean life span of DBA2 mice bearing L1210 leukemia (up to 24%), animals do not survive beyond this time. Treatment with P-Gly-Phe-Leu-Gly-ADR (5 mg/kg) consistently increased mean survival time, and in addition produced survivors at 50 days (up to 80% surviving). Polymers containing in addition galactosamine or fucosylamine were equally effective. Degradation of the drug-**polymer linkage** was a prerequisite for pharmacol. activity, P-Gly-Gly-ADR was totally ineffective. Conjugation of ADR limited toxicity, a >10 fold increase in dose could be given in the polymer-bound form without obvious ill effect. Measurement of the pharmacokinetics of 125I-labeled HPMA copolymer-ADR conjugates showed a marked alteration from the pattern of distribution reported previously for free ADR, and the levels of radioactivity detected in the heart were extremely low. The latter observation supports the observed decrease in toxicity seen for conjugated drug.

L36 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

1988:267388 Document No.: PREV198886006632; BA86:6632. ANTICANCER AGENTS COUPLED TO N-2 HYDROXYPROPYLMETHACRYLAMIDE COPOLYMERS II. EVALUATION OF DAUNOMYCIN CONJUGATES IN-VIVO AGAINST L1210 LEUKEMIA. DUNCAN R [Reprint author]; KOPECKOVA P; STROHALM J; HUME I C; LLOYD J B; KOPECEK J. DEP BIOLOGICAL SCI, UNIV KEELE, KEELE, STAFFORDSHIRE ST5 5BG, UK. British Journal of Cancer, (1988) Vol. 57, No. 2, pp. 147-156. CODEN: BJCAAI. ISSN: 0007-0920. Language: ENGLISH.

AB DBA2 mice were inoculated i.p. with 105L1210 cells. Animals subsequently treated with daunomycin (single i.p. dose, 0.25-5.0 mg kg-1) all died. The maximum increase in mean survival time observed was .apprx. 135%. Animals treated with N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers conjugated to daunomycin (DNM) showed a significant increase in mean survival time when the **polymerdrug linkage** was

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biodegradable (i.e., Gly-Phe-Leu-Gly). Such treatment also produced a number of long term survivors (> 50 days). In contrast, HPMA copolymer conjugated to DNM via a non-degradable linkage (Gly-Gly) produced no increase in survival time relative to untreated control animals. The effect observed with **biodegradable** HPMA copolymer-DNM conjugates was dependent on the concentration of conjugated drug administered (optimum > 5 mg kg-1); the frequency of administration (multiple doses were more effective than single); the timing of administration (single doses given on days 1 and 3 were most effective); and the site of tumor inoculation and route of drug administration. **Biodegradable** HPMA copolymer-DNM conjugates administered i.p. were active against L1210 inoculated s.c. at higher doses than required to curb a peritoneal tumor. Under certain experimental conditions polymer-DNM conjugates containing fucosylamine or galactosamine proved more active than conjugates without the carbohydrate moiety. The mechanism of drug-conjugate action in vivo is at present unclear. Radioiodination of polymer showed .apprx. 75% of polymerdrug conjugate to be excreted 24 h after i.p. administration. Synthesis of HPMA conjugates containing [3H]DNM showed that polymer containing Gly-Gly-[3H]DNM was excreted (60% of radioactivity in the urine, 24 h) in macromolecular form. In contrast polymer containing Gly-Phe-Leu-Gly-[3H]DNM was largely excreted in the form of low molecular weight species.

L36 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 3

89240328 Document Number: 89240328. PubMed ID: 3508536. Coupling of naltrexone to **biodegradable** poly(alpha-amino acids). Negishi N; Bennett D B; Cho C S; Jeong S Y; Van Heeswijk W A; Feijen J; Kim S W. (Department of Pharmaceutics, University of Utah, Salt Lake City 84112.) PHARMACEUTICAL RESEARCH, (1987 Aug) 4 (4) 305-10. Journal code: 8406521. ISSN: 0724-8741. Pub. country: United States. Language: English.

AB The narcotic antagonist naltrexone (I) was modified at the 3 and 14 hydroxyl positions and covalently coupled to a **biodegradable** poly(alpha-amino acid) backbone through a labile bond. Selective acetylation of I with acetic anhydride gave naltrexone-3-acetate (II), which was subsequently succinoylated to naltrexone-3-acetate-14-hemisuccinate (III) with succinic anhydride. The polymeric backbone chosen for initial coupling experiments was poly-N5-(3-hydroxypropyl)-L-glutamine (PHPG). The side-chain hydroxyl functionality permitted covalent bonding of III through an ester linkage. Hydrolysis of covalently bound drug to give naltrexone or its derivatives (II and III) should be much slower than diffusion of drug through the polymer matrix. While hydrolysis of naltrexone from the polymer side chain is first order, release of drug from the matrix can be zero order due to the geometry of the device and the physical and chemical interactions between naltrexone and the polymer matrix. In vitro studies of PHPG-naltrexone conjugate in disk form did not show constant release because of the hydrophilic nature of the polymer backbone and the changing local chemical environment upon hydrolysis of drug-**polymer linkages**. The conjugated system was made more hydrophobic by coupling drug to copolymers of hydroxypropyl-L-glutamine (HPG) and L-leucine. Conjugates of III coupled with copoly(HPG-70/Leu-30) demonstrated a nearly constant, but slightly declining release rate of naltrexone and its derivatives for 28 days in vitro.

L36 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 4

86077544 Document Number: 86077544. PubMed ID: 4074638. Poly-L-aspartic acid as a carrier for doxorubicin: a comparative in vivo study of free and polymer-bound drug. Pratesi G; Savi G; Pezzoni G; Bellini O; Penco S; Tinelli S; Zunino F. BRITISH JOURNAL OF CANCER, (1985 Dec) 52 (6) 841-8. Journal code: 0370635. ISSN: 0007-0920. Pub. country: ENGLAND: United

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Kingdom. Language: English.

AB The synthetic polypeptide, poly-L-aspartic acid (PAA, mol. wt = 20,000) has been used as a macromolecular carrier for doxorubicin. The drug may be released in vivo through hydrolysis of the ester linkage formed between the carboxyl groups of the polymer and the drug side chain. PAA has been found to be a suitable carrier since it is a soluble, **biodegradable**, multivalent and nontoxic polymer. The toxicity and the therapeutic efficacy of free and **polymer-linked** doxorubicin have been evaluated in normal and tumour-bearing mice, using a variety of experimental tumour systems. In studies on single and multiple drug administration, the results indicated that the polymeric derivative of doxorubicin had approximately 3-fold lower toxicity than did free drug. In addition, the severity of specific toxic effects, including cardio- and vesicant toxicity, were appreciably reduced following conjugation to PAA. The doxorubicin-PAA conjugate gave similar or rather greater therapeutic effects than free drug at less toxic doses. This effect, more evident in the highly sensitive tumours, suggests an improvement of the therapeutic index of the **polymer-linked** drug.

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